Chiral switches of chloroquine and hydroxychloroquine: potential drugs to treat COVID-19

Ilaria D'Acquarica*[1] and Israel Agranat*[2]

[1] Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, Rome, Italy. E-mail: ilaria.dacquarica@uniroma1.it

[2] Organic Chemistry, Institute of Chemistry, The Hebrew University of Jerusalem, Edmond J. Safra Campus, Jerusalem 9190401, Israel. E-mail: isri.agranat@mail.huji.ac.il

"Repurposing" of chloroquine and hydroxychloroquine against COVID-19

Therapeutic options in response to the COVID-19 pandemic are urgently needed [1]. A keyword in these worldwide efforts is "repurposing", the development of approved antiviral drugs as candidates for COVID-19. Chloroquine (**CQ**) and its hydroxyl analogue hydroxychloroquine (**HCQ**) are showing preliminary inhibitory effects against COVID-19 and apparent efficacy in clinical studies [2,3]. We propose a variant of the "repurposing" strategy, i.e., developing single enantiomers of these old *racemic* drugs. We call for urgently pursuing the chiral switches of **HCQ** and/or **CQ** for the treatment of COVID-19.

Chloroquine phosphate (**CQ phosphate**), IUPAC name: N^4-(7-chloro-4-quinolinyl)-N^1,N^1-diethylpentane-1,4-diamine diphosphate and hydroxychloroquine sulfate (**HCQ sulfate**), IUPAC name: 2-[[4-[(7-chloro-4-quinolinyl)amino]pentyl]ethylamino]ethanol sulfate are old antimalarial drugs approved by FDA in 1949 and 1955, respectively (Fig. 1) [Drugs@FDA]. **HCQ sulfate** has also been approved for rheumatoid arthritis (RA), lupus erythematosus (LE) and other autoimmune diseases.

The activity as immune modulators exerted by **CQ**/**HCQ** suggested their potential use in the treatment of human infections (namely, bacterial, fungal and viral) which are often associated with inflammation and/or immune activation. In vitro activity of **CQ/HCQ** has been reported for a wide range of viruses, including HIV, where **CQ** showed a broad-spectrum anti-HIV-1 and HIV-2 in vivo activity achieved by inhibition of viral particle glycosylation and synergism with protease inhibitors. Several studies have shown the capability of **CQ phosphate** to inhibit replication also of coronaviruses, a large family of RNA viruses that usually cause mild to moderate upper-respiratory tract diseases, among which there is the severe acute respiratory syndrome (SARS)-associated coronavirus. In these studies, **CQ** proved to inhibit SARS-CoV replication on Vero E6 cells with EC_{50} in the low-micromolar interval, ranging from 4.1 to 8.8 μM [4]. Notably, **CQ** was found to be effective in preventing replication also of SARS-CoV-2 at an EC_{50} value of 1.13 μM [3]. **HCQ** has just been reported to efficiently inhibit COVID-19 infection in vitro (Liu, J. et al., *Cell Discovery*, April 2020).

In anticipation of increased demand for **CQ phosphate** and **HCQ sulfate**, the FDA is taking steps to ensure that adequate supply of these drug products is available by publishing product-specific guidances (PSGs) to support generic drug development for these drugs (Docket No. FDA-2007-D-0369, 13 April 2020).

CQ and HCQ through the looking glass: the importance of chirality

CQ and **HCQ** are chiral drugs administered as racemates, i.e., consisting each as a 1:1 mixture of two paired enantiomers, namely (*S*)-(+) and (*R*)-(–) (Fig. 1). The chirality of drugs has become a major theme in the design, discovery, development, patenting and marketing of new drugs [5]. For many years, including at the time of the approvals of **CQ** and **HCQ**, the pharmacopoeias were dominated by racemates. This trend was inverted in the mid-1990s: the majority of the chiral new molecular entity (NME) drugs have been developed and marketed as single enantiomers [5]. The strategy of chiral switches has emerged - the development of a single enantiomer from a chiral drug that has previously been developed (and often approved and marketed) as a racemate or as a mixture of diastereomers. Nevertheless, the development and approval of racemic drugs has continued to be viable and the continuing approval of racemic NMEs could have implications for the persistence of the chiral-switch strategy [6].

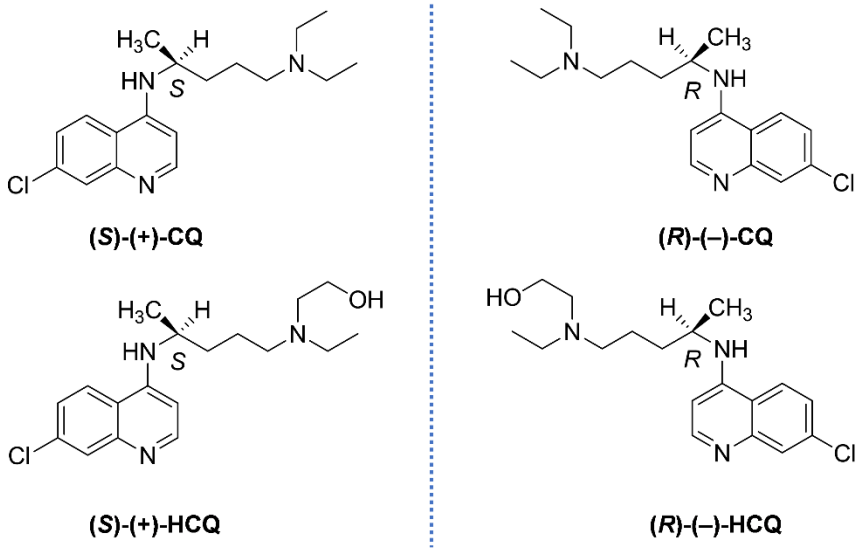

Figure 1. Chemical structures of the paired (*S*)-(+) and (*R*)-(–) enantiomers of chloroquine (**CQ**) and hydroxychloroquine (**HCQ**). CAS Numbers: **(*S*)-(+)-CQ**: [58175-86-3]; **(*R*)-(–)-CQ**: [58175-87-4]; **(*S*)-(+)-HCQ**: [137433-24-0]; **(*R*)-(–)-HCQ**: [137433-23-9].

According to the EMA guidelines for the development of a new single enantiomer from an approved racemate [7], suitable “bridging” studies should be carried out to link the complete racemate data to the incomplete data on the selected enantiomer. The extent of bridging studies should be defined on a case-by-case basis.

The chiral switch of **HCQ** was initiated indeed in the early 1990s, with method of use patents US 5,314,894 (priority date 15-09-1992, assignee Sterling Winthrop, Inc., New York) and EP 0588430B1 claiming the enantiomer (*S*)-(+)-hydroxychloroquine (**(*S*)-(+)-HCQ**) for treatments of malaria, RA and LE. However, these initiatives and earlier and subsequent studies on **HCQ** and **CQ** enantiomers have not led to regulatory single-enantiomer drug approval(s) for any indication. The Sterling Winthrop portfolios of **CQ** and **HCQ**, including the pharmacological studies of the two enantiomers, were probably transferred to SANOFI (proprietor of EP 0588430B1) in June 1994.

Developing (*S*)-(+)-HCQ, the more-promising enantiomer

We aim preferentially at (*S*)-(+)-hydroxychloroquine (**(*S*)-(+)-HCQ**), the more-promising enantiomer (Patents US 5,314,894 and EP 0588430B1, proprietor SANOFI, priority date 15-09-1992, now expired), followed by (*S*)-(+)-chloroquine (**(*S*)-(+)-CQ**). The rationale on which our call is based is driven by the following considerations. COVID-19 is a pandemic without any approved drug or vaccine. **CQ** and **HCQ** may potentially display therapeutic efficacy for the treatment of COVID-19 [2,3,8]. The toxicity profiles of **CQ** and **HCQ** have been well known for many years; their administration is safe, although both can have serious side effects, especially at high doses or when combined with other medicines. Advantages of **(*S*)-(+)-HCQ** (the eutomer) vis-à-vis **(*R*)-(–)-HCQ** and the racemate **(*R*,*S*)-(±)-HCQ** have been recorded in the above-mentioned patents, especially with regard to retinopathy, a severe side effect of **HCQ** which is due to an enantioselective accumulation of the **(*R*)-(–)-HCQ** enantiomer in the ocular tissue, *R*/*S* ratio = 1.58 ± 0.24 (in rabbits, EP 0588430B1). Furthermore, studies of enantioselectivity in the pharmacokinetics of **HCQ** reported that there was no **(*S*)-(+)-HCQ** ⇌ **(*R*)-(–)-HCQ** interconversion between the enantiomers [9].

The pointed clinical implications of using the **(*S*)-(+)-HCQ** "substantially free" of the **(*R*)-(–)-HCQ** as active ingredient were lower adverse effects and the possibility of higher dose levels and/or longer periods of administration. Various syntheses of the enantiomers of **HCQ** and **CQ** have been reported, including a simple method of synthesis for large-scale production of the CQ enantiomers (Patent CN 105693605B, priority date 09-03-2016). Urgent guidance for navigating and circumventing the QTc interval prolongation and torsadogenic potential side effects of **HCQ** and **CQ** potential therapies for COVID-19 are noted [10].

According to the EMA guidelines [7] (*vide supra*), it would be productive in the present case (namely, **(*S*)-(+)-HCQ**) to use data on the corresponding racemate (i.e., **HCQ**), as far as is applicable to the enantiomer. Under the highly demanding, urgent circumstances, relaxations of the regulations are needed. FDA has just created the Coronavirus Treatment Acceleration Program (CTAP) to speed up coronavirus therapies and move new treatments to patients as quickly as possible. EMA indicated that it will be flexible and pragmatic during the assessment of affected clinical trial data submitted to the Agency as part of marketing authorization applications. Hopefully, the "bridging" studies (*vide supra*) will be reduced, in consultation between the sponsor and the regulator, in order to shorten the development and approval periods.

On 17 March 2020, the Italian Medicines Agency (AIFA) expressed a favorable opinion on including the off-label use of **CQ** and **HCQ** for the treatment of COVID-19 pandemic. On 28 March 2020, FDA issued an Emergency Use Authorization (EUA) to allow **HCQ sulfate** and **CQ phosphate** products donated *pro bono publico* by leading pharmaceutical companies to the U.S. Strategic National Stockpile (SNS) to be distributed and used for certain hospitalized patients with COVID-19.

Emergency drug approvals of **(*S*)-(+)-HCQ** and/or **(*S*)-(+)-CQ** should be considered. Government agencies in major jurisdictions may also take up the challenge. It has not escaped our minds that the incentives of regulatory and secondary patent exclusivities may be diminished in the current crisis. However, a successful chiral switch of **HCQ** may be rewarded. SANOFI, the owner of the portfolios of **CQ** and **HCQ**, is in a preferred position to purse the chiral switch. Philanthropic foundations may also be recruited for the cause of overcoming the COVID-19 pandemic.

Conclusion

Our call for “repurposing” **HCQ** and/or **CQ** by urgently developing the chiral switches of these racemates to their (*S*)-(+)-enantiomers for the treatment of COVID-19 is based on the expectations of safer pharmacological profiles of the selected enantiomers, favourable risk to benefit profiles, and shortened development and approval processes. Demand for **HCQ** has grown dramatically in recent weeks as a result of the attention raised by the CTAP program. The further step that we propose here, taking into account the necessary vigilance and risk management, is the switch to **(*S*)-(+)-HCQ**, the more-promising single enantiomer of a known drug which proved safe and well tolerated in most patients.

References

[1] Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020; 19: 149-50.
[2] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020; 16: 72-3.
[3] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269-71.
[4] Colson P, Rolain J-M, Lagier J-C, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int J Antimicrob Agents, 2020; (in press).
[5] Calcaterra A, D’Acquarica I. The market of chiral drugs: chiral switches versus de novo enantiomerically pure compounds. J Pharm Biomed Anal 2018; 147: 323-40.
[6] Agranat I, Wainstein SR, Zusman E. The predicated demise of racemic new molecular entities is an exaggeration. Nature Rev Drug Discov 2012; 11: 972-73.
[7] Investigation of Chiral Active Substances 3CC29a, previously EU III/3501/91. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002816.pdf (last accessed April 20, 2020).
[8] Colson P, Rolain J-M, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. Int J Antimicrob Agents 2020; 55: 105923.
[9] Ducharme J, Fieger H, Ducharme MP, Khalil SKW, Wainer IW. Enantioselective disposition of hydroxychloroquine after a single oral dose of the racemate to healthy subjects. Br J Clin Pharmacol 1995; 40: 127-33.
[10] Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc prolonging and torsadogenic potential of possible pharmacotherapies for COVID-19 [published online ahead of print March 25, 2020]. *Mayo Clin. Proc.* https://doi.org/10.1016/j.mayocp.2020.03.024.

Declaration of conflict of interest

The authors declare no conflict of interest.